DETAILED ACTION

Receipt of Amendments/Remarks filed on March 19 2010 is acknowledged. Claims 1-24, 26, 44 and 46 were/stand cancelled. Claims 25, 38 and 45 were amended. Claims **25, 27-43, 45 and 47-48** are pending.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25, 27-43, 45 and 47-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 25 and 45 introduce new matter as the claims recite the limitation: "wherein the microemulsion composition is free of a carrier of the oil-soluble

drug". There is no support in the specification for this limitation. The limitation of: "free of a carrier of the oil-soluble drug" was not described in the specification as filed, and person skilled in the art would not recognize in the applicant's disclosure a description of the invention as presently claimed. Applicants have indicated support from the amendment comes from paragraph 3 of the published specification. While this paragraph lists four specific carriers, this paragraph does not provide support for the idea that the microemulsions of the invention are free of a carrier of the oil-soluble drug. The instant specification provides no definition for the term carrier. Therefore, the instant specification provides no guidance as to what components are contemplated as being excluded from the microemulsion. Furthermore, the drugs that are taught as being oil soluble drugs are those which possess little solubility in water. This does not mean that no amount of the drug is soluble in water just that a very small amount of drug is soluble in water. Therefore, water would be interpreted as a carrier for at least the percentage of the drug that dissolved. Furthermore, claim 42 recites that the oil soluble drug is a mixture of the base form and the salt form of the drug. However, the specification indicates (page 19) that the salt form of the drugs have much greater solubility in the aqueous phase. Therefore, when the drug is present in salt form based on Applicants own teachings, water is serving as a carrier and would therefore have to be excluded but it is a specifically recited phase. Since water is clearly contemplated and exemplified in the microemulsion compositions instantly claimed, it is the Examiner's position that the disclosure does not reasonably convey that the inventor

had possession of the subject matter of the amendment at the time of filing of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 25, 27-30, 34, 37-38, 40-41, 43 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hauer et al. (US Patent No. 6024978, cited in the Office action mailed on 6/12/08) as evidenced by The Merck Index (1989, cited in the Office action mailed on 6/12/08) is **withdrawn** in light of Applicants' amendments and arguments filed on 3/19/10.

The rejection of claims 31-33, 39 and 45 under 35 U.S.C. 103(a) as being unpatentable over Hauer et al. in view of Constantinides et al. (WO 9408610, cited on PTO Form 1449) is **withdrawn** in light of Applicants' amendments and arguments filed on 3/19/10.

The rejection of claims 35-36 and 42 under 35 U.S.C. 103(a) as being unpatentable over Hauer et al. as evidenced by The Merck Index (1989, page 1364, cited in the Office action mailed on 6/12/08) in view of The Merck Index (1989, page 478, cited in the Office action mailed on 6/12/08) is **withdrawn** in light of Applicants' amendments and arguments filed on 3/19/10.

Claims 25, 27-41, 43, 45 and 47-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glen et al. (US Patent No. 4798846) in view of Constantinides et al. (WO 9408610, cited on PTO Form 1449).

Applicant Claims

The instant application claims a microemulsion comprising an oil phase and an aqueous phase wherein the oil phase comprises an oil-soluble drug, a long chain

polymer surfactant and a short chain fatty acid surfactant wherein the microemulsion is free of a carrier of the oil-soluble drug. The particle size of the oil phase is from 10 nm to 100 nm (0.01 to 0.1 μm or 100 to 1000 angstroms).

The instant application claims a microemulsion comprising an oil phase and an aqueous phase wherein the oil phase comprises an oil-soluble drug; and an emulsifier combination comprising a long chain polymer surfactant and a short chain fatty acid surfactant wherein the microemulsion is free of a carrier of the oil-soluble drug. The particle size of the oil phase is from 10 nm to 100 nm (0.01 to 0.1 μm or 100 to 1000 angstroms).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Glen et al. is directed to pharmaceutical compositions. The invention relates to pharmaceutical compositions which may be administered parenterally to a warm-blooded animal for the production of general anesthesia (column 1, lines, 7-10). One embodiment is a composition which is an oil in water emulsion in which the 2,6-diisoproopylphenol either alone or dissolved in a water-immiscible solvent and is emulsified with water by means of a surfactant (column 1, lines 53-59). Examples of surfactants include ethoxylated fatty acids, those derived from polyethoxylated sorbitan and a fatty acid such as Tween, polyoxyethylene-polyoxypropylene block copolymers such as Pluronics (aka poloxamers). Specific surfactants taught include Tween 20, 40, 60, 80, Cremophor, and Pluronic F68 (columns 1-2, lines 60-68 and 1-20). The amount of surfactant ranges from 2 to 30% by weight of the composition and 0.1 to 5% by weight of 2,6-diisopropylphenol (column 2, lines 46-50). The composition may optionally

contain one or more additional constituents such as stabilisers, preservatives or antioxidants (column 2, lines 66-68). The compound, 2,6-diisopropylphenol, produces smooth and rapid anesthesia when injected intravenously as a composition of the invention (column 3, lines 40-42). Exemplified surfactants include, Tween 20, 40, 60, 80 and Pluronic F68. The examples are taught as being micro-emulsions. It is specifically taught that the resulting emulsion is repeatedly passed through a homogeniser until a suitably low particle size is formed (example 7).

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

While Glen et al. teach the form of the composition can be that of a micro-emulsion and that passage through a homogeniser until a suitably low particle size is formed, Glen et al. does not specify the particle size of the micro-emulsion. While Glen et al. teach the composition can comprise an antioxidant, Glen et al. does not specify the incorporation of tocopherol. However, these deficiencies are cured by Constantinides et al.

Constantinides is directed to microemulsions comprising an oil, a mixture of high and low HLB surfactants (abstract). It is disclosed that it has been long recognized that low interfacial tension contributes to the thermodynamic stability of microemulsion. To achieve this, the surfactant should preferably exhibit low solubility in both the oil and water phases and be preferentially absorbed at the water-oil interface with concomitant lower of the interfacial tension. An interfacial tension of less than $2x10^{-2}$ dyn/cm results in stable microemulsions (page 1, lines 23-28). It is taught that there are many advantages to the use of a microemulsion over conventional emulsions for drug

transport. Microemulsions form spontaneously, without the need for a high input of energy and therefore easy to prepare and scale up for commercial applications. They have thermodynamic stability due to their small particle size and therefore have a long shelf life; they have an isotropically clear appearance so that they may be monitored by spectroscopic means; they have relatively low viscosity and are therefore easy to mix. (page 2, lines 9-22). It is disclosed that the incorporation of medium-chain fatty acid salts have been found to further enhance the absorption of a biologically active agent (page 5, lines 29-30). Medium chain is defined as fatty acyl chain having from 6 to 12 carbon atoms (page 5, lines 36-37). A particular combination of high HLB surfactant combination exemplified is Tween 80 and sodium laurate (example 7). It is disclosed that high HLB surfactants such as the medium chain fatty acids and Tween 80 (which is indicated by Applicant as being a suitable long chain fatty acid surfactant (page 16 of the specification)) are present in an amount from about 5 to about 75% (page 15, lines 5-7). Constantinides indicates that one of skill in the art would know that in order to accommodate a larger amount of a hydrophilic phase then this will have be matched by an increase in the relative amount of high HLB surfactant (page 15, lines 13-16). The diameter of droplets or particles of the microemulsions are less than 150 nm, preferably less than 100 nm, and most preferably in the range of 5 to 35 nm (page 16, lines 8-11). The compositions can comprise optional ingredients such as antioxidants such as tocopherol (page 16, lines 18-20).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Glen et al. and Constantinides et al. and utilize sodium laurate in combination with another high HLB surfactant such as Tween 80 or Pluronic F68. One of ordinary skill in the art would have been motivated to utilize sodium laurate in combination with another high HLB surfactant as medium chain fatty acid salts have been found to further enhance the absorption of biologically active agents as taught by Constantinides et al.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Glen et al. and Constantinides et al. and to optimize the amount and ratio of the high HLB surfactants present in the microemulsion. One of ordinary skill in the art would have been motivated to optimize the amount and ratio depending on the surfactants utilized as the well as the amount of a hydrophilic phase. Constantinides et al. indicate that a larger amount of a hydrophilic phase results in a higher requirement of a high HLB surfactant needed, therefore, the smaller the hydrophilic phase the less high HLB surfactant is needed. Therefore, the amount and ratio of surfactants in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results. It would have been obvious to one of ordinary skill in the art at the time of the invention to engage in routine experimentation to determine optimal or

workable ranges that produce expected results. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Aller, 220 F. 2d 454, 105 USPQ 233 (CCPA 1955).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Glen et al. and Constantinides et al. and utilize a droplets or particles of the microemulsions less than 150 nm. One of ordinary skill in the art would have been motivated to utilize a microemulsion as Glen et al. teach and exemplify microemulsion formulations and Constantinides et al. teach that microemulsions have many advantages over conventional emulsions such as they form spontaneously and therefore are easy to prepare and scale up. Therefore, one of ordinary skill in the art would have been motivated to formulate a microemulsion due to their many advantages and utilize a particle size of less than 150 nm, which is a taught particle size of a microemulsion, based on the teachings of Constantinides et al.

Regarding the claimed long chain polymer surfactant component, Pluronic F68 (page 15 of the specification) and Tween 80 (page 16 of the specification)) are taught as a suitable long chain polymer surfactant.

Regarding the interfacial tension, Glen et al. is silent as to the interfacial tension. Constantinides disclosed that it has been long recognized that low interfacial tension contributes to the thermodynamic stability of microemulsion. To achieve this, the surfactant should preferably exhibit low solubility in both the oil and water phases and be preferentially absorbed at the water-oil interface with concomitant lower of the

interfacial tension. An interfacial tension of less than $2x10^{-2}$ dyn/cm results in stable microemulsions (page 1, lines 23-28). Therefore, when desiring a stabile microemulsion it would have been obvious to one of ordinary skill in the art to select surfactants that exhibit low solubility in both oil and water phases as taught by Constantinides.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Glen et al. and Constantinides et al. and add the antioxidant tocopherol to the microemulsion. One of ordinary skill in the art would have been motivated to add tocopherol as Glen et al. teach that the composition can include antioxidants as Constantinides et al. teach that antioxidants known include tocopherol. Therefore, it would have been obvious to one of ordinary skill in the art to add tocopherol for it's antioxidant effect.

Regarding claim 47, since it would have been obvious to add tocopherol, the addition of tocopherol results in a composition comprising two oil soluble drugs (tocopherol and propofol).

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicants argue that (1) the Office action does not set forth a common sense reason to combine the teachings of Glen and Constantinides. Constantinides teaches a composition wherein the biologically active material refers to materials that are soluble in the hydrophilic phase. It is argued that because Glenn teaches composition with a sparingly soluble in water biologically active agent the biologically active agents taught in Glen are different than those found in Constantinides.

Applicants' arguments filed March 19 2010 have been fully considered but they are not persuasive.

While the biologically active agents taught are different, that is not why the examiner utilized Constantinides. Constantinides teaches that the surfactants with a high HLB have been found to increase absorption of the biological agent. The examiner maintains that one of ordinary skill in the art would have a reasonable expectation that this would also be true of low water soluble drugs. As evidence, Crison et al. (US Patent No. 5993858) which is directed to formulations with lipophilic, poorly water soluble active drug or ingredient teach that surfactants with a high HLB increase the bioavailability of lipophilic drugs (column 5, lines 40-45 and column 6 lines 18-30). Therefore, while Constantinides may be directed to water soluble drugs, one of ordinary skill in the art would have been motivated to utilize the teachings of Constantinides and add a high HLB surfactant such as sodium laurate in combination with another high HLB surfactant such as Tween 80 or Pluronic F68. One of ordinary skill in the art would have been motivated to utilize sodium laurate in combination with another high HLB

surfactant as medium chain fatty acid salts have been found to further enhance the absorption of biologically active agents as taught by Constantinides et al.

New Rejections Necessitated by the Amendments filed March 19 2010

Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Glen et al. in view of Constantinides et al. and in further view of The Merck Index (1989, page 478, cited in the Office action mailed on 6/12/08).

Applicant Claims

The instant application claims that the drug is a mixture of the base form and the salt form of the drug.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Glen and Constantinides et al. are set forth above. Hauer et al. is to the delivery of propofol an anesthetic. Constantinides et al. teach that high HLB surfactants enhance the absorption of biologically active agents

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

Glen et al. do not specify that the drug is a mixture of the base form and the salt form of the drug. However, this deficiency is cured by The Merck Index.

The Merck Index indicates that dibucaine which is a local anesthetic is available as the hydrochloride salt as well the base form. The structure of dibucaine contains an aryl group.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Glen et al., Constantinides and The Merck Index and utilize dibucaine in the microemulsion. One of ordinary skill in the art would have been motivated to add dibucaine because it is an anesthetic agent just like propofol. As a general principle it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose, the idea of combining them flows logically from their having been individually taught in the prior art. See *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) **MPEP 2144.06.**

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Glen et al., Constantinides and The Merck Index and utilize both the base form and salt form of the anesthetic. One of ordinary skill in the art would have been motivated to utilize this form because both forms are known and the incorporation of both forms would allow for the increased solubility of the drug as the base form would be more oil soluble while the salt form would be more water soluble.

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ABIGAIL FISHER whose telephone number is (571)270-3502. The examiner can normally be reached on M-Th 9am-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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